UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,427	03/09/2006	Jung-Hyun Kim	5252YU-1	3355

22442 7590 06/08/2009

SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
06/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,427	KIM ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10-12 and 14* is/are pending in the application.

4a) Of the above claim(s) *1,2,4-7 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8,10,11 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 3/26/2009, which incorporates the Remarks of the response of 12/12/2008, have been received and entered into the application file.

Claims 8 and 11 have been amended; claims 3, 9 and 13 have been cancelled; new claim 14 has been added. Claims 1, 2, 4-7 and 12 remain withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions, there being no allowable generic or linking claim. Election was made **without** traverse on 5/7/2008. Claims 1, 2, 4-8, 10-12 and 14 remain pending. Claims 8, 10, 11 and 14 have been considered on the merits.

Priority

Acknowledgment is made that the instant application is a national stage entry under 35 USC 371 of international application PCT/KR04/00054, filed 1/11/2005.

The international application appears to have made a priority claim to Korean application 10-2003-0002314, filed 1/14/2003. A certified copy of the Korean application has been received in the instant application from WIPO. However, the national stage of the instant application does not contain a proper claim to the foreign priority document under 35 USC 119(b) and 37 CFR § 1.55, as no reference is made in the declaration, or in an application data sheet, to the foreign application. Currently there is NO RECOGNIZED CLAIM FOR FOREIGN PRIORITY.

Oath/Declaration

The oath or declaration is still defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the foreign application for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application having a filing date before that of the application on which priority is claimed, by specifying the application number, country, day, month and year of its filing.

It appears the declaration submitted 3/9/2006 erroneously claimed foreign priority, under 35 USC 119(a)-(d) to the international application PCT/KR04/00054, instead of to the Korean application 10-2003-0002314. The error can be corrected by supplying an application data sheet in accordance with 37 CFR § 1.76(c).

Response to Arguments/Amendments

Applicants' remarks, filed 12/12/2008 have been fully considered. Each point will be addressed below, as appropriate. Rejections/objections not repeated herein have been withdrawn.

Please note cancellation of claims 9 and 13 have rendered all rejections thereof moot.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to provide enablement for the full scope of the claims. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new ground of rejection necessitated by the addition of claim 14.

The specification is found enabling for a method of preparing a biological tissue, wherein a biological tissue is defined as an aggregate of cells with their intracellular substance that form one of the

structural components (See "Tissue" Merriam-Webster Online Dictionary, 2009). Such a biological tissue may be considered suitable for regeneration of a tissue based on the same cell type provided within the biological tissue (i.e. a biological tissue seeded with chondrocytes may be considered suitable for regeneration of cartilage tissue; a biological tissue seeded with osteocytes may be considered suitable for regeneration of bone tissue; etc); however the specification does not reasonably provide enablement for preparing a biological tissue which is capable of regenerating a complete organ selected from the group consisting of heart, lung and liver. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue or unreasonable experimentation. See *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). The key word is 'undue,' not experimentation.' " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all these factors are considered, a sufficient number are discussed below so as to create a prima facie case.

The scope of claim 14 reads on a method of preparing a biological tissue which is suitable as a replacement for one of the heart, lung or liver of an individual. A fully functional tissue engineered organ must have mechanical and biochemical properties of natural organs; thus the biological tissue which is to

be a replacement for the heart, lungs or liver must exhibit all mechanical and biochemical properties of these complete organs.

The specification provides a single example wherein chondrocytes are seeded onto/into porous scaffolds and are reported to proliferate *in vitro* and upon implantation *in vivo*. There are no examples wherein replacement hearts, lungs or livers are produced.

At the time the invention was made the field of tissue engineering was well developed. The basic theory of tissue engineering is applying the physiologically relevant type of cell to a supporting matrix material to replicate the function of the tissue which is to be replaced; this technique has been applied to virtually every organ system in the body with varying degrees of success. For example, Marler et al (Advanced Drug Delivery Reviews, 1998) reviews works on development of liver tissue, intestinal tissue, urologic tissues, skin, cartilage, bone and cardiovascular structures which have application in regeneration of corresponding natural tissues (See Marler et al, Pgs. 169-179). However, despite promising results with small-sized tissue constructs, a major limitation of development of larger tissue constructs (such as whole organs) is development of a sufficient microvascular system (See Laschke et al, Tissue Engineering, 2006, page 2094). Without vasculature, tissue constructs can be no more then a few cells thick, otherwise cells farthest away from the surface (and the culture medium) become necrotic. While various teams have proposed methods for inducing angiogenesis or for developing vasculature systems which may be included, these techniques remain theoretical in nature, as no reproducible methods have been widely accepted. Thus, effective methods of providing sufficient vasculature to engineered tissue constructs were not recognized at the time the invention was made, and work is still ongoing to realize the theoretical approaches (See Laschke et al, Pg. 2099). Therefore, development of full replacement organs, such as heart, lung and liver, were not recognized as feasible in the art at the time of the filing of the instant invention.

Due to the fact that there was little success in the art regarding vascularization of tissue

constructs, and the art recognized this field as critical to tissue engineering, yet not achievable based on the then present technology, a large amount of guidance and teachings would need to presented in the instant disclosure to support a claim to production of full tissue engineered organs which can replace the heart, lungs, and liver.

Guidance and teachings provided by Applicants in the instant specification is limited to disclosure that the biological tissues produced by the claimed method can be used in regeneration of one of the heart, lung and liver organs. There are no examples, working or prophetic, of heart, lung or liver tissues, much less full organs. The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, discussed above, which recognizes that vascularization of tissue engineered constructs is necessary for survival, yet methods of achieving the necessary levels of vascularization were beyond the skill level at the time of the invention, and limited teachings in the instant disclosure with regards to development of full organs which can replace or regenerate the heart, the lungs, or the liver, the Office would require appropriate disclosure to support the contention that the current method can successfully yield replacement organs for the heart, lungs and liver. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, due to the high level of unpredictability in the art, the current specification would have to provide greater amounts of teachings and guidance directed to methods of carrying out the claimed invention.

Therefore, due to the sum of all the aforementioned factors, one of ordinary skill in the art, at the time the invention was made, would not expect success carrying out the claimed method of preparing a biological tissue that is suitable for regeneration of the heart, the lung or the liver organs. Given that the art fails to recognize and Applicant has failed to demonstrate production of such intricate tissue construct, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to

practice the claimed invention using any species of stem cell. Accordingly, claim 14 is deemed properly rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicants have amended the claims in order to comply with 35 USC 112, second paragraph. The amendments substantially obviate the rejections previously of record. The following rejections are applied to the claims as currently amended:

Claims 8, 10, 11 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have amended claim 8 to overcome substantially all the issues previously raised under 35 USC 112, second paragraph. However, it remains that gelatin, one of the disclosed species of 'semi-permeable agents' is not chemically cross-linked; thus it is unclear how the semi-permeable membrane is to be cross-linked gelatin.

Claim 8 is newly rejected because of the phrase "to form by the cross-linking thereof, a semi-permeable membrane, permeable to nutrients, on an overall outer surface of each of the scaffolds…" The metes and bounds of "an overall outer surface of each of the scaffolds" cannot be determined.

The dependent claims inherit the deficiencies of independent claim 8, and thus are rejected on the same grounds.

Claim 11 is rejected for reciting the trademarked brand Teflon®. If a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not

comply with the requirements of the 35 U.S.C. 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). It would be remedial to recite the chemical name "polytetrafluoroethylene."

Claim 14 is rejected as indefinite because it appears to recite a broad limitation followed by a narrower limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14 recites the broad recitation loading a plurality of said scaffold pieces into a molding container "having a predetermined form and size," and the claim also recites "[the container has] a morphology of a tissue to be regenerated" which is the narrower statement of the range/limitation. It is not clear that the predetermined form and size *is that of* a morphology of the tissue to be regenerated, rather the claim defines the container as having 1) a predetermined form and size (broad limitation), and 2) a morphology of a tissue to be regenerated (narrower limitation).

Claim 14 is further rejected as indefinite because, in the step of adding a semi-permeable agent, it is unclear what forms the biodegradable polymer construct. The claim recites adding a semi-permeable agent (i.e. a material that will form a semi-permeable material upon cross-linking) and a cross-linking

agent to a molding container to interconnect the plurality of scaffold pieces *to form* a biodegradable polymer construct. No polymer material has previously been recited, it is not clear what the biodegradable polymer construct comprises (i.e. does the combination of the scaffolds and the semi-permeable material formed by the cross-linking of the 'semi-permeable agent' form the biodegradable polymer construct? does the semi-permeable material formed by the cross-linking of the 'semi-permeable agent' constitute the biodegradable polymer construct alone?)

Furthermore, in claim 14 it is unclear what is necessary to cause interconnection of the scaffold pieces, as the claim recites that such interconnection occurs upon addition of the cross-linking agent (lines 8-9), after a period of 1 to 20 minutes (lines 13-14), and after introduction of nutrients (lines 15-16). It is not clear what step actually achieves the interconnection. Clarification is required.

Still further, claim 14 is rejected because it is unclear what is meant by the prepared biological tissue being suitable for neovascularization ("…wherein the biological tissue prepared is suitable for one of the following:…neovascularization…"). Does this mean that the tissue would promote neovascularization? If so, where? (i.e. in an extant tissue or organ? In a tissue engineered construct?) Or does this mean that the tissue, itself, is vascularized? Understanding of how the tissue construct is suitable for neovascularization affects what types of cells would be provided to the scaffolds; thus clarification is required in order to define the metes and bounds of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicants have traversed the rejection under 35 USC 103(a) over Zaleske et al in view of Bouhadir et al on the grounds that Zaleske et al fails to disclose addition of a cross-linking agent, and that Teflon would not have been an obvious substitute for a Petri dish, unless one relies on impermissible hindsight.

In response to Applicants' argument that Zaleske et al fail to disclose a cross-linking agent, it is respectfully submitted that the rejection is based on the fact that Zaleske et al disclose calcium alginate hydrogel as a species of gel which may be used to coat the cartilage unit (See Zaleske et al, claim 3); and that it was known in the art that calcium alginate gel is formed by combining alginate and calcium chloride (See Bouhadir et al). Therefore, though Zaleske et al does not specifically disclose applying alginate (as the semi-permeable agent) and calcium chloride (as the cross-linking agent) one of ordinary skill in the art would have recognized that both materials would have been necessary for formation of the calcium alginate gel, and thus applied.

In response to Applicants' argument that the substitution of Teflon for the Petri dish is only arrived at through use of impermissible hindsight, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case Bouhadir et al specifically disclose Teflon containers for use with calcium alginate gels, therefore Teflon molds and containers were taught in the art for the purpose of supporting calcium alginate gels and forms, and was not found only in the instant disclosure. It is further noted that Applicants' current claims 8, 10 and 11 do not require the container to give form *to the* biological tissue, but rather only require that the container have a predetermined shape and form *suitable for formation of* the biological tissue. This merely requires the container to be of a shape and form that can physically

support the biological tissue, both Petri dishes and the Teflon molds disclosed by Bouhadir et al would be considered *suitable for formation* of a biological tissue, in fact any non-toxic container that has a solid base would be considered suitable for forming a biological tissue. Therefore, the rejection is maintained as proper, and takes into account only what was disclosed in the cited references, and information generally available to the artisan of ordinary skill at the time the invention was made, hindsight reasoning was not improperly relied upon.

Claims 8, 10 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zaleske et al (US Patent 6,183,737), in view of Bouhadir et al (Biotechnol Prog. 2001).

Zaleske et al disclose methods of forming a cartilage implant, which reads on the biological tissue as currently claimed. The cartilage implant may be formed by providing two or more non-viable cartilage matrices in apposition, seeding the two or more matrices with isolated chondrocytes to form a cartilage construct, and then applying a biological gel to the cartilage construct to fill gaps at the interface of the two or more cartilage pieces. Alternatively, the individual non-viable cartilage matrices may be seeded with isolated chondrocytes prior to being held in apposition (See Zaleske et al, col. 2, ln 11-33). The cartilage construct may then be implanted *in vivo* (See Zaleske et al, col. 6, ln 16-24).

In their example, Zaleske et al disclose co-culturing chondrocytes with three non-viable cartilage matrices; loading the cell-seeded matrices onto a sterile Petri dish, such that the three matrices are stacked upon one another; applying fibrin glue around the stack of cell-seeded matrices to form a composite cartilage unit; and then implanting the cartilage unit in subcutaneous pockets in nude mice (See Zaleske et al, col. 5, ln 45-col. 6, ln 24).

The non-viable cartilage matrices are considered to read on the scaffolds of the instant invention, thus the step of seeding chondrocytes onto the non-viable cartilage matrices reads on the step of 'seeding cells obtained from a tissue to be regenerated onto one or more scaffolds', it is noted the source of the

cells (*i.e.* "from a tissue to be regenerated") is a product-by-process limitation. Process limitations are considered only insofar as the method of production imparts distinct structural or chemical characteristics or properties to the product. In the case of the source of the cells, it is noted that source of the cells does not impart any unique structural characteristics to the cells, thus chondrocytes obtained from any source satisfy the limitation of the current claim.

The Petri dish is considered to read on the molding container, having a predetermined size and form suitable for forming the biological tissue, of the instant invention. It is noted the claim does not require the predetermined size and form of the molding container to correlate in any manner to the size and form of the biological tissue being produced, but rather only for the container to be *suitable for* forming the biological tissue. A Petri dish is considered *suitable for* forming a biological tissue, as it provides a physical base on which the tissue can be produced. Thus, the step of loading the cell-seeded matrices into a sterile Petri dish is considered to read on the step of ' loading the scaffold seeded with the tissue cells into a molding container with a predetermined shape and size suitable for forming the biological tissue.'

The step of implanting the cartilage unit *in vivo* is considered to read on introducing nutrients into the scaffold interconnected with the semi-permeable membrane thereby proliferating the tissue cells to produce a biological tissue. Upon implantation *in vivo* the cartilage unit is exposed to nutrients (i.e. blood, growth factors, tissues, etc) in the body; Zaleske et al report that upon recovery the cartilage unit exhibits cellular maturation (See Zaleske et al, col. 8, ln 20-67).

The exemplified method of Zaleske et al differs from the instant invention in that they apply fibrin glue as the biological gel to adhere the cartilage matrices and to fill gaps at the interface(s) between matrices. While the fibrin glue may be considered a semi-permeable agent that forms a semi-permeable

membrane on an outer surface of each of the scaffolds, Zaleske et al does not teach further adding a cross-linking agent, as fibrin does not require cross-linking.

However, it is submitted that, at the time the invention was made, it would have been obvious to one of ordinary skill in the art to alternatively use a calcium alginate gel in place of the fibrin glue, as fibrin glue and calcium alginate gel were both disclosed as suitable biological gels which may be used in the method of Zaleske et al (See Zaleske et al, col. 3, ln 63-col. 4, ln 5). Calcium alginate gel is formed by cross-linking alginate with calcium chloride (See, e.g. Bouhadir et al, Pg. 946, col 1 "Hydrogel Formation and Degradation"), thus to use calcium alginate gel as the biological gel, one would apply alginate, and then calcium chloride to the appositioned scaffolds in the method of Zaleske et al. Alginate reads on the 'semi-permeable agent', calcium chloride reads on the cross-linking agent. Suitability of calcium alginate gel for use with chondrocytes and cartilage implants is further supported by Bouhadir et al. Bouhadir et al disclose using calcium alginate gel (formed by cross-linking alginate with calcium chloride) to form substrates for culturing chondrocytes (See Bouhadir et al, Pg. 946, col. 1 "Hydrogel Formation and Degradation").

Zaleske et al further differs from the instant invention in that they utilize Petri dishes as the 'molding container', not Teflon containers. However, it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art to select any known container which is capable of providing a physical base on which the cartilage unit of Zaleske et al may be assembled as the container. Particularly when the fibrin glue is being replaced with calcium alginate gel, as suggested above, one would have found it obvious to select a Teflon mold based on the teachings of Bouhadir et al. Bouhadir et al report using Teflon molds to form the calcium alginate gels (See Bouhadir et al, pg. 946, col. 1). Teflon is a non-stick surface, thus the calcium alginate gels are easily removed from the Teflon containers without sticking. Therefore, it is submitted that use of Teflon molds as a support structure for holding or

otherwise supporting the biological tissue in the method of Zaleske et al would have been obvious because, again, the substitution of one known element for another (Teflon for Petri dishes) would have yielded the predictable result of successfully holding the construct, thereby rendering the invention obvious to one of ordinary skill in the art at the time the invention was made.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 10, 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Awad et al (US 2005/0288796), in view of Bouhadir et al (Biotechnology Progress, 2001). This is a new ground of rejection necessitated by the addition of claim 14.

Awad et al disclose methods for producing biological tissues which may be used in applications of soft tissue regeneration.

In their examples Awad et al discloses methods for producing biological tissues which may be used in cartilage regeneration. The method comprises: obtaining cartilage tissue, pulverizing, decellularizing, sterilizing and lyophilizing the cartilage tissue to produce a composition comprising a plurality of individual devitalized native soft tissue matrices (NSTM-CH). The collection of NSTM-CH are provided in a polypropylene tube (See Awad et al, Example 1, paragraphs 0047-0050).

At the point-of-care cells are applied to the composition of lyophilized NSTM-CH to produce a cell/NSTM-CH suspension. The cells may be selected from chondrocytes, mesenchymal stem cells, adipose derived stem cells or other chondroprogenitor cell (See Awad et al, Example 7, paragraph 0060 & paragraphs 0040-0041). The cells may be derived from tissues which the construct is intended to treat (See Awad et al, paragraph 0028).

The cell/NSTM-CH suspension is then mixed with a pharmaceutical grade hydrogel at an appropriate concentration. The hydrogel is preferably an *in situ* cross-linkable material, such as agarose

pluronic F-127, collagen, alginate, or fibrin. Alginate is preferred. (See Awad et al, Example 7 paragraph 0060).

In the method of Awad et al the NSTM-CH are considered to read on the plurality of scaffold pieces as currently claimed. Application of cells to the NSTM-CH is considered to read on the step of seeding cells from a tissue to be regenerated onto the scaffold pieces.

The hydrogel is considered to read on the semi-permeable membrane which serves to interconnect the individual NSTM-CH scaffold pieces to form a 'biodegradable polymer construct'.

The step of implanting the biodegradable polymer construct is considered to read on providing nutrients to the construct to proliferate the cells and to permit interconnecting of the scaffold pieces into a biological tissue.

The exemplified method of Awad et al differs from the method instantly claimed in that Awad et al do not provide the details regarding size, material concentrations, set-up times or disclosure of particular container materials. However, in reading the method of Awad et al one of ordinary skill in the art would have found it *prima facie* obvious to optimize these parameters through routine experimentation to determine the appropriate or working ranges (times, concentrations, suitable containers, etc) to successfully carry out the method of Awad et al; in such optimization, one would have found the instant invention *prima facie* obvious.

First, regarding the size of the individual NSTM-CH particles (scaffolds): Awad et al disclose the cartilage should be pulverized to particles sized >800 microns (>0.8 mm) (See Awad et al, paragraph 0049). The instant claims appear to require that the individual scaffolds have a diameter ranging from 1-3 mm. This difference in size of the individual particles is not found to support patentability because the size of the cartilage particles (NSTM-CH particles/scaffolds) may be manipulated based on the size of the

defect to be treated, the type of cells to be seeded thereupon, and the type of tissue from which the NSTM is derived. Therefore, the artisan of ordinary skill would have found it *prima facie* obvious to experiment with different NSTM particles sizes, even slightly outside the range suggested by Awad et al, in order to optimize the biological tissue construct for the specific application at hand. Means of manipulating the particle size of the NSTM were well within the technical grasp of the artisan, and involve merely reducing or increasing the duration or degree of grinding or milling.

Second, regarding the step of 'loading the plurality of scaffolds into a molding container having a predetermined shape and size and having a morphology of a tissue to be regenerated': Awad et al disclose the NSTM-CH pieces are provided in a polypropylene tube (See Awad et al, paragraph 0047-0050), this is considered to read on a loading a plurality of scaffolds into a container having a predetermined size and form, and depending on the morphology of the tissue site to be treated, the tube may be considered to have a morphology of the tissue to be regenerated. However, it is further submitted that Awad et al state the material may be provided in a moldable carrier or be fabricated by casting the hydrogel into a mold (See Awad et al, paragraphs 0030 and 0037). Furthermore, it is submitted that use of Teflon containers would have been *prima facie* obvious based on their disclosed use in the method of Bouhadir et al. Like Bouhadir et al, Awad et al disclose alginate hydrogel may be used as the hydrogel; Bouhadir et al report use of Teflon molds for use with alginate hydrogels, as they are non-stick and thus permit recovery of the alginate hydrogels without deformation (See Bouhadir et al, pg. 946, col. 1). Therefore, it is submitted that use of Teflon molds as the container or mold in the method of Awad et al would have been obvious because the substitution of one known element for another (Teflon for polypropylene tubes) would have yielded the predictable result of successfully containing the construct comprised of the plurality of scaffold pieces surrounded by a hydrogel, thereby rendering the invention obvious to one of ordinary skill in the art at the time the invention was made.

Third, regarding the formation of the hydrogel 'semi-permeable membrane': Awad et al do disclose a number of cross-linkable materials which may be utilized to form the viscous hydrogel carrier, including agarose, collagen, and alginate, alginate being preferred (See Awad et al, Example 7). Though Awad et al do not disclose that calcium chloride is added as the cross-linking agent, it is submitted that one of ordinary skill in the art would have understood that calcium chloride is routinely used to cross-link alginate to form a calcium alginate hydrogel (See, e.g. Bouhadir et al). Concentrations of the alginate and calcium chloride would be routinely optimized to achieve the desired viscosity. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, there is no evidence of record to support that the claimed concentrations of alginate (the semi-permeable agent) or calcium chloride (the cross-linking agent) are critical or otherwise unexpected; therefore the claimed values are held as *prima facie* obvious. Similarly it is submitted that the porosity of the alginate hydrogel can be routinely controlled by manipulating the concentration and molecular weight of the alginates (See, e.g. Bouhadir et al) and by post-formation modification, such as freeze-drying (See Awad et al, paragraph 0037).

Fourth, regarding a set-up time for the implant material prior to use: it is noted that Awad et al do not disclose a specific waiting period in which the hydrogel is permitted to set-up; however, it is submitted that the need to permit a hydrogel to set-up prior to handling would have been recognized as *prima facie* obvious by one of ordinary skill in the art, the exact duration would depend on the viscosity, the volume of hydrogel present, the air temperature, humidity and the degree of exposed surface area of the hydrogel to the air, thus the time would be routinely optimized to suit the specific conditions.

Fifth, and finally, regarding the step of adding nutrients to the construct: Awad et al discloses implanting the construct into a tissue defect, this is considered to read on adding nutrients to the construct, as blood and bodily fluids contain nutrients that are thus delivered to the construct; however it would alternatively have been *prima facie* obvious to one of ordinary skill in the art to supply nutrients, such as culture medium, *in vitro* for purposes of observing cell growth and differentiation for research purposes. Therefore, as a whole, the differences between the prior art method of Awad et al and the instantly claimed method are not sufficient to support non-obviousness of the instant invention, rather the method of Awad et al discloses the general method as currently claimed, and details such as concentrations, duration of culture, and container shapes, are found to be *prima facie* obvious over the knowledge of one of ordinary skill in the art. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651